Exhibit B

Pharmacokinetics

SECOND EDITION, REVISED AND EXPANDED

Milo Gibaldi
University of Washington
School of Pharmacy
Seattle, Washington

Donald Perrier
School of Pharmacy
University of Arizona
Tucson, Arizona

MARCEL DEKKER
MARCEL DEKKER, INC. NEW YORK • BASEL

Determination of C_{max} and t_{max}

Mathematical relationships can be developed to estimate the time at which a peak plasma concentration of drug should be observed and the maximum plasma concentration at this time following first-order input into the body. Expanding Eq. (1.94) yields

$$C = \frac{k_a F X_0}{V(k_a - K)} e^{-Kt} - \frac{k_a F X_0}{V(k_a - K)} e^{-k_a t} \tag{1.102}$$

which when differentiated with respect to time gives

$$\frac{dC}{dt} = \frac{k_a^2 F X_0}{V(k_a - K)} e^{-k_a t} - \frac{k_a K F X_0}{V(k_a - K)} e^{-Kt} \tag{1.103}$$

When the plasma concentration reaches a maximum (C_{max}) at time t_{max}, $dC/dt = 0$. Therefore,

$$\frac{k_a^2 F X_0}{V(k_a - K)} e^{-k_a t_{max}} = \frac{k_a K F X_0}{V(k_a - K)} e^{-Kt_{max}} \tag{1.104}$$

which reduces to

$$\frac{k_a}{K} = \frac{e^{-Kt_{max}}}{e^{-k_a t_{max}}} \tag{1.105}$$

Taking the logarithm of both sides of Eq. (1.105) and solving for t_{max} yields

$$t_{max} = \frac{2.303}{k_a - K} \log \frac{k_a}{K} \tag{1.106}$$

For a given drug, as the absorption rate constant increases, the time required for the maximum plasma concentration to be reached decreases.

The maximum plasma concentration is described by substituting t_{max} for t in Eq. (1.94):

$$C_{max} = \frac{k_a F X_0}{V(k_a - K)} \left(e^{-Kt_{max}} - e^{-k_a t_{max}}\right) \tag{1.107}$$

However, a simpler expression can be obtained. From (1.105) it can be shown that

$$e^{-k_a t_{max}} = \frac{K}{k_a} e^{-Kt_{max}} \tag{1.108}$$

Substituting for $e^{-k_a t_{max}}$, according to (1.108), in (1.107) yields

$$C_{max} = \frac{k_a F X_0}{V(k_a - K)} \frac{k_a - K}{k_a} e^{-Kt_{max}} \tag{1.109}$$

which is readily simplified to

$$C_{max} = \frac{FX_0}{V} e^{-Kt_{max}} \tag{1.110}$$

The values of C_{max} and t_{max} under the special circumstance when $k_a = K$ is of mathematical interest and will be considered briefly. Under these conditions, Eq. (1.92) can be written as

$$\overline{X} = \frac{KFX_0}{(s + K)^2} \tag{1.111}$$

Hence

$$X = KFX_0 te^{-Kt} \tag{1.112}$$

$$C = \frac{KFX_0 te^{-Kt}}{V} \tag{1.113}$$

and

$$\log C = \log \frac{KFX_0 t}{V} - \frac{Kt}{2.303} \tag{1.114}$$

Equation (1.114) indicates that when $k_a = K$, a semilogarithmic plot of C versus t will contain no linear segments.

Differentiating Eq. (1.113) with respect to time yields

$$\frac{dC}{dt} = \frac{KFX_0}{V} e^{-Kt} - \frac{K^2 FX_0}{V} te^{-Kt} \tag{1.115}$$

At t_{max}, $C = C_{max}$ and $dC/dt = 0$. Therefore,

$$\frac{KFX_0}{V} e^{-Kt_{max}} = \frac{K^2 FX_0}{V} t_{max} e^{-Kt_{max}} \tag{1.116}$$